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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/760,048	TSANG ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-23* is/are pending in the application.

4a) Of the above claim(s) *1-9, 11, 13-17, 21 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,18-20 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II and SEQ ID NO: 7 in the reply filed on September 5, 2006 is acknowledged. The traversal is on the ground(s) that the primers of the present invention are designed to operate as pairs in order to achieve exponential amplification. Applicants further assert that the primers share common subject matter and are interwoven so as to constitute a single invention. The response also asserts that the courts encourage patentees to make a more detailed disclosure of their discoveries and thereby it is in the interest of the public for a patentee to claim all aspects of an invention.

These arguments have been fully considered but are not found persuasive because the restriction requirement did not prevent applicants from claiming all aspects of the invention. Rather, Applicants election and formatting of the claims limited the subject matter to the individual primer sequence of SEQ ID NO: 7. As set forth in the election requirement, Applicant was required to elect a single nucleic acid or a particular combination of nucleic acids (e.g., a primer pair). Thereby, Applicants had the opportunity to elect a first primer of SEQ ID NO: 7 and a second primer of SEQ ID NO: 5, together with the adapter primers of SEQ ID NO: 9 and 10. If Applicant had elected this particular combination of primers, then claims which required the use of each of these specific nucleic acids would have been examined. Further, Applicants arguments are not persuasive because each of the claims do not require the use of a second primer. Rather, independent claims 10 and 19 are drawn to methods which require the

use of a primer consisting essentially of SEQ ID NO: 7 and optionally a sequence required for a selected amplification reaction. These claims do not require the use of a second primer. Additionally, the primers of SEQ ID NO: 5 and 7 (and SEQ ID NO: 9 and 10) do not share "common subject matter" because each of these primers consists of a different nucleotide sequence and hybridizes to a distinct target nucleotide sequence. Thereby, restriction between the primers having distinct structures and functions is proper.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 10, 18, 19, 20, and 22, directed to the elected invention, i.e., methods for detecting enteroviruses using the primer of SEQ ID NO: 7 have been examined herein. Note that claims 19, 20, and 22 have been examined only to the extent that the claims read on the elected invention of SEQ ID NO: 7. The subject matter of SEQ ID NO: 5 (and SEQ ID NO: 9 and 10) is withdrawn from consideration as being drawn to a non-elected invention. These claims should be amended in response to this Office action so that the claims are limited to the elected invention.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10, 18, 19, 20, and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10, 18, 19, 20, and 22 are indefinite for failing to recite a clear nexus between the preamble of the claims and the final process step of the claims. The claims are drawn to methods for detecting an enterovirus. However, the final step is one for detecting an amplified target. The claims do not set forth a clear relationship between the detection of an amplified target and the detection of an enterovirus. Accordingly, it is unclear as to whether the claimed method is one for detecting any sequence amplified using the primer of SEQ ID NO: 7 or one for detecting an enterovirus.

Claims 10, 18, 19, 20, and 22 are indefinite over the recitation of "consisting essentially of the target binding sequence of SEQ ID NO: 7 and , optionally, a sequence required for a selected amplification reaction" because it is unclear as to what is intended to be the relationship between SEQ ID NO: 7 and the optional sequence. For instance, it is unclear as to whether SEQ ID NO: 7 and the optional sequence are separate nucleic acids or are attached to one another. If the sequences are attached to one another, it is unclear as to whether the optional sequence may be present at either the 3' end or the 5' end of SEQ ID NO: 7 and it is unclear as to the means by which the nucleic acids are attached – e.g., through a linker or through a phosphate bond etc. the claims are also indefinite over the recitation of "selected amplification reaction" since the claims and specification do not set forth the criteria for selecting the amplification reaction and it is unclear as to whether the selected amplification reaction is the same or distinct from the amplification reaction used to amplify the target sequence.

Claims 10, 18, 19, 20, and 22 are indefinite over the recitation "the target binding sequence" because this phrase lacks proper antecedent basis. This rejection may be overcome by amendment of the claims to recite "**a** target binding sequence."

Claim 18 is indefinite over the recitation of "the oligonucleotide" because this phrase lacks proper antecedent basis.

Claim 20 is indefinite. To the extent that the claim reads on the elected invention, the claim encompasses a method in which both the first amplification primer and the second amplification primer consist essentially of the sequence of SEQ ID NO: 7. It is unclear as to the distinction between the first and second amplification primer. Further, since the claim recites only that the method further comprises a second amplification primer, the claim does not clearly set forth how the second amplification primer is utilized in the method for detecting an enterovirus.

Claim 22 is indefinite over the recitation of "the sequence required for the selected detection reaction" lacks proper antecedent basis because the claims do not previously refer to any particular sequence that is required and do not previously refer to any particular selected detection reaction. Accordingly, it is unclear as to what constitutes the sequence that is required for a selected detection reaction.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10, 18, 19, 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable Yoon (WO 03/014397) in view of Nycz (Analytical Biochemistry. 1998. 259: 226-234)).

Yoon (page 7, line 24 through page 8, line 17) teaches methods for detecting enterovirus nucleic acids wherein the methods comprise amplifying a target nucleic acid sequence using a first amplification primer to produce an amplified target nucleic acid and detecting the amplified target nucleic acid as indicative of the presence of an enterovirus nucleic acid. The reference (pages 10-11) teaches that the method is one for detecting all enteroviruses, including coxsackie viruses, polioviruses, echoviruses, and enteroviruses 68, 69, 70 and 71. The reference (pages 10-11) also teaches that each enterovirus shares a genotype specific region which consists of nucleotides 164 to 526 of the 5' UTR. In particular, Yoon (page 11, 22 and 23 and Table 3) exemplifies methods wherein amplification of enteroviruses is performed using an EV2 primer which

consists of conserved sequences of the 5'UTR. The EV2 primer of Yoon contains a nucleotide sequence that is identical to the EV2 target binding sequence present in instant SEQ ID NO: 7:

EV2 primer of Yoon: ATTGT**CACCATAAGCAGCC**A

sequence of SEQ ID NO: 7: CACCATAAGCAGCC

Yoon does not teach detecting enterovirus nucleic acids using a primer which consists essentially of the full length sequence of SEQ ID NO: 7.

However, present SEQ ID NO: 7 is an SDA (strand displacement amplification) primer, which includes 3 regions: a) a first 3' region that is complementary to an enterovirus target binding sequence; b) a BsoBI restriction enzyme site 5' of the target binding sequence and which consists of the sequence of CTCGGG; and c) a 5' sequence that is not complementary to the target sequence and which consists of the sequence of CGATTCCACTCCAGACTT.

Methods for detecting target RNA sequences using SDA primers, as well as SDA primers containing 3' target binding regions, restriction enzyme sites, and 5' non-target binding regions, were well known in the art at the time the invention was made, and are specifically taught by Nycz.

Nycz (page 226) teaches methods for detecting a target RNA sequence comprising amplifying a target sequence using a first amplification primer to produce an amplified target nucleic acid and detecting the amplified target nucleic acid as indicative of the presence of the target RNA sequence. In particular, the amplification primer consists of three regions: a) a first 3' region that is complementary to a target binding

sequence; b) a restriction enzyme site 5' of the target binding sequence; and c) a 5' sequence that is not complementary to the target sequence (see col. 2, lines 58-67 through col. 3, lines 1-18). Nycz (page 227) teaches that the method is applicable to the detection of any RNA target and specifically exemplifies methods which detect HIV target nucleic acids.

In the method of Nycz (page 227), the amplification primer contains a BsoBI restriction enzyme site consisting of nucleotides CTCGGG, and a 5' non-target binding sequence of CGATTCCGCTCCAGACTT. Thereby the 5' non-target binding sequence of Pearson differs from that present in SEQ ID NO: 7 by a single nucleotide:

5' non-target region of Pearson: CGATTCC**G**CTCCAGACTT

5' non-target region of SEQ ID NO: 7: CGATTCC**A**CTCCAGACTT

Nycz (page 226) also teaches that SDA is an isothermal amplification method that provides greater than 10^{10} -fold amplification in 15 minutes. The reference (page 226) characterizes the disclosed method of quantitative RT-SDA as being "ideally suited for viral quantification because of its simple workflow, fast time to result and freedom from sophisticated equipment."

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Yoon so as to have amplified the enterovirus nucleic acids using the RT-SDA method of Nycz in order to have achieved the advantages clearly set forth by Nycz of providing a highly sensitive, rapid, simple and time effective method for detecting enterovirus nucleic acids. Such a modification of the method of Yoon would have resulted in the requirement to modify the

EV2 primer of Yoon so that the primer was suitable for the RT-SDA reaction. The resulting primer would thereby have included the BsoBI restriction enzyme site 5' of the target binding sequence and would have further included a 5' non-target binding sequence. While the 5' non-target binding sequence of Nycz differs from that of SEQ ID NO: 7 at one internal nucleotide, modification of the sequence of the 5' non-target binding region of the primer of Nycz to obtain additional 5' non-coding sequences, including the 5' non-target binding sequence of SEQ ID NO: 7, would have been obvious to one of ordinary skill in the art at the time the invention was made. Optimization of the sequences of the 5' region to select sequences which did not hybridize with the target sequence and which would hybridize at a similar Tm and work most efficiently in combination with additional primers would have been well within the skill of the art at the time the invention was made since the parameters which effect primer annealing, particularly with respect to SDA methods, were well known in the art. Accordingly, in the absence of evidence to the contrary modification of the 5' non-target sequence of Nycz to obtain the 5' non-coding sequence 5-'GATTCCACTCCAGACTT-3' would have been obvious to one of ordinary skill in the art and well within the skill of the art.

Further, modification of the primer of Yoon so as to have generated additional primers for the detection of enterovirus, and particularly modification of the primer of Yoon so as to have omitted the 5' terminal 6 nucleotides, would have been obvious to one of ordinary skill in the art. Designing primers which are equivalents to those taught in the art is routine experimentation. The parameters and objectives involved in the

selection of primers were well known in the art at the time the invention was made. Moreover, software programs were readily available which aid in the identification of conserved and variable sequences and in the selection of optimum primer pairs. The prior art is replete with guidance and information necessary to permit the ordinary artisan to design additional primers for the amplification of enterovirus. Additionally, Yoon specifically teaches that nucleotides 164 to 526 of the 5'-UTR of enteroviruses are highly conserved and that additional primers of varied lengths could be obtained from this region (see pages 10-11). Thereby, the ordinary artisan would have had more than a reasonable expectation of success of obtaining additional primers for amplifying enterovirus sequences. Thus, for the reasons provided above, the use of primers of SEQ ID NO: 7 in an RT-SDA method for detecting enterovirus would have been obvious to one of ordinary skill in the art.

Additionally, it is noted that the claims recite the language "consisting essentially of." Since this phrase has not been clearly defined in the specification and because there is no art recognized definition for this phrase as it applies to nucleic acids, the phrase has been interpreted as meaning that additional nucleotides may be present at either the 3' end or 5' end of the primer. To the extent that the claims encompass primers consisting of the sequence of SEQ ID NO: 7, additional modification of the primer of Yoon so as to have omitted the 3' nucleotide would have also been obvious to one of ordinary skill in the art in view of the teachings of Yoon and in the prior art of the sequences of enterovirus nucleic acids and methods for generating additional primers for detecting enterovirus nucleic acids. Thereby, in the absence of evidence to the

contrary, use of SDA primers consisting of SEQ ID NO: 7 in the method for detecting enterovirus would have been obvious to one of ordinary skill in the art and well within the skill of the art.

Regarding claim 18, Yoon does not teach detecting the amplified target nucleic acids using a labeled probe. However, Nycz (figure 1 and page 228) teaches that in the RT-SDA method, the primers are unlabeled and the target sequence is detected using a labeled probe complementary to the amplified target sequence. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Yoon so as to have contacted the amplified target nucleic acids with a labeled probe in order to have facilitated the detection of the hybridization complex formed between the amplified target nucleic acid and probe, thereby providing an effective means for detecting the enterovirus nucleic acids.

Regarding claim 20, the claim does not distinguish between the first and second amplification primer. Thereby, the claim has been interpreted as including a single step of amplifying the target nucleic acid using SEQ ID NO: 7 as the first and second amplification primer.

Regarding claim 22, the resulting SDA-primer as set forth above includes a restriction site fro facilitating the detection of the amplified target sequence.

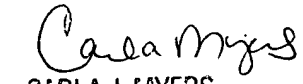
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach

the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
Art Unit 1634



CARLA J. MYERS
PRIMARY EXAMINER